The Restriction Requirement

Applicants herein confirm the election for further prosecution in this case the claims of Group I, namely Claims 1-14. This election is made without traverse.

Sequence Compliance

The Examiner indicates that the present application is not in compliance with the sequence listing rules. In response and in adherence with 37 C.F.R. §§ 1.821-1.825, this amendment is accompanied by a floppy disc containing the nucleotide and amino acid sequences, SEQUENCE ID NUMBERS 1-14 in computer readable form, and a paper copy of the sequence information. The computer readable sequence listing was prepared through use of the software program "PatentIn" provided by the PTO.

Applicants submit that the information contained in the computer readable disc is identical to that of the paper copy. The sequence listing contains no new matter.

Applicant submits that submission of the accompanying computer readable sequence listing, and the paper copy thereof serve to place this application in a condition of adherence to the rules 37 C.F.R. §§ 1.821-1.825.

Objections to the Specification

The title of the application is objected to as not being descriptive of the claimed invention. In response, Applicants have amended the title of the invention as suggested by the Examiner, thereby obviating the objection to the specification.

The Rejection under 35 U.S.C. § 112, First Paragraph

Claims 1-14 stand rejected under 35 U.S.C. § 112, first paragraph, as the specification, while enabling for VEGF antagonists comprising a mutation of a cysteine residue of the native VEGF protein, allegedly does not reasonably provide enablement for functional derivatives of VEGF antagonists.

Without necessarily agreeing with the propriety of the outstanding rejection, Applicants have herein amended the pending claims to delete reference to "functional derivatives". Applicants, therefore, believe that the rejection has been overcome and respectfully request its withdrawal.

The Rejection under 35 U.S.C. § 112, Second Paragraph

Claims 1-14 stand rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite for failing to particular point out and distinctly claim the subject matter which applicants regard as the invention. Specifically, the Examiner asserts that the phrase "VEGF antagonist molecule" is unclear because the abbreviation "VEGF" may mean different things in the art.

In response, Applicants have amended Claim 1 to replace the first occurrence of "VEGF" with "vascular endothelial cell growth factor (VEGF)". It is respectfully submitted that this amendment serves to obviate then outstanding rejection.

The Rejections under 35 U.S.C. § 102

Claims 1, 2, 10-13 and 14 stand rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by Claffey et al. Applicants respectfully traverse the rejection.

The presently claimed invention is directed to antagonists of VEGF activity. As is recited in the claims, these VEGF antagonists are VEGF polypeptides having one or more mutated cysteine residues which inhibit the molecules from properly dimerizing. However, as is explicitly recited in the claims, these molecules retain the ability to bind to the VEGF receptor. It is this property that makes them effective as antagonist molecules, i.e., their ability to bind to and occupy a VEGF receptor, thereby preventing wild-type VEGF from binding to that receptor and activating VEGF activity.

Claffey et al. teach a variety of murine VEGF mutants that are incapable of inducing VEGF activity. Specifically, in Figure 7, Claffey et al. demonstrate that a variety of cysteine residue mutants of VEGF have no biological activity. However, what is notable about the Claffey et al. disclosure is that it does not teach, suggest nor even contemplate that these mutant VEGF molecules would retain the ability to bind to the VEGF receptor and, thereby effectively function as a VEGF antagonist as presently claimed. In this regard, the Examiner must

keep in mind that for a mutant VEGF polypeptide to function as an antagonist molecule as presently claimed, it must be able to bind to and occupy the VEGF receptor. The Claffey et al. article does not teach this.

The Examiner, however, asserts that Claffey et al. show in Figure 7 that some of the VEGF cysteine mutants "appear to have some stimulatory activity" and, therefore, must bind to the VEGF receptor. Applicants respectfully disagree. In this regard, Applicants note that the VEGF activities shown in Figure 7 have a possible error rate of about 5% as compared to wild-type VEGF activity (see page 7, column 2, lines 18-23 of the Claffey et al. article). Thus, the results shown in Figure 7 for the C25-S, C56-S and C67-S mutants are not statistically significant.

Applicants also note that the authors of the Claffey et al. article state:

> "The results indicate that non-dimerizing single chain VPF mutants C25-S and C67-S have essentially no microvascular permeability-enhancing activity despite appreciable levels of protein production." (See page 7, column 2, lines 11-15, emphasis supplied).

Thus, the authors of the Claffey et al. actually confirm that these mutants have no biological activity.

In light of the above, Applicants respectfully submit that one of ordinary skill in the art could not determine from the Claffey et al. article that any VEGF mutant disclosed therein retains the ability of binding to the VEGF receptor, thereby making it an effective VEGF antagonist molecule as presently claimed. As such, Claffey et al. do not teach "each and every" element of the presently claimed invention and, therefore, do not anticipate the presently claimed invention under 35 U.S.C. § 102(b). In this regard, Applicants respectfully

direct the Examiner to In re Bond, 15 USPQ2d 1566, 1567 (Fed. Cir. 1990), where the Federal Circuit stated "[f]or a prior art reference to anticipate in terms of 35 U.S.C. § 102, every element of the claimed invention must be identically shown in a single reference." (Emphasis added). Applicants, therefore, respectfully request reconsideration and withdrawal of the outstanding rejection.

Claims 1-3, 10-12 and 14 stand rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by Pötgens et al. Applicants respectfully traverse the rejection.

The Examiner asserts that Pötgens et al. teach in Figure 8 that various cysteine residue mutants of VEGF are capable of binding to VEGF receptors. Applicants respectfully disagree. Figure 8 of the Pötgens et al. article presents the results of an assay whereby cells were incubated with either (1) radiolabeled wild-type VEGF alone or (2) radiolabeled wild-type VEGF in combination with an unlabeled VEGF mutant polypeptide. The results presented in Figure 8 demonstrate that various cysteine residue VEGF mutants are capable of inhibiting the binding of radiolabeled wild-type VEGF to the surface of the cells as evidenced by a reduction in the amount of radioactivity bound to the surface of the cells).

The Examiner assumes herein that the reduction in the amount of radiolabeled wild-type VEGF to the surface of the cells in the presence of an unlabeled cysteine residue mutant is a result of that mutant's ability to bind to the VEGF receptor, thereby displacing the radiolabeled wild-type VEGF therefrom. However, the results presented in Figure 8 of the Pötgens et al.

article could just as well be due to the ability of the mutant polypeptide to bind to the radiolabeled wild-type VEGF polypeptide, and not to the VEGF receptor, thereby preventing the radiolabeled wild-type polypeptide from binding to it receptor. Such a mechanism would result in a reduction in the amount of radiolabeled wild-type VEGF polypeptide binding to the cell surface, exactly as is shown in Figure 8 of the Pötgens et al. article.

In light of the above, Applicants respectfully submit that Pötgens et al. do not teach that their cysteine residue mutants are capable of binding to VEGF polypeptides and, thereby functioning as effective VEGF antagonist molecules. Therefore, Applicants respectfully request reconsideration and withdrawal of the outstanding rejection under 35 U.S.C. § 102.

The Rejections under 35 U.S.C. § 103

Claim 13 stand rejected under 35 U.S.C. § 103 as allegedly being unpatentable over Pötgens et al. Claims 4-6 and 9 stand rejected under 35 U.S.C. § 103 as allegedly being unpatentable over Pötgens et al. Finally, Claims 7 and 8 stand rejected under 35 U.S.C. § 103 as allegedly being unpatentable over Pötgens et al. in view of Pang. Applicants respectfully traverse the rejections.

In traversal, Applicants again note that Pötgens et al. do not teach that their cysteine residue mutants are capable of binding to VEGF receptors and, therefore, do not teach that their mutant VEGF polypeptides are capable of functioning an effective VEGF antagonists.

Moreover, nothing in the Pötgens et al. article teaches or suggests to one of ordinary skill in the art how to go about obtaining VEGF antagonist molecules that retain the ability to bind to VEGF receptor, thereby functioning as antagonists of VEGF activity. Only in the present application was it demonstrated that VEGF antagonists which retain the ability to bind to and occupy VEGF receptors could be obtained.

Additionally, the cited Pang reference does nothing to remedy the above described defect of the Pötgens et al. article. Pang teaches or suggests nothing about the ability to obtain VEGF antagonist polypeptides which retain the ability to bind to and occupy VEGF receptors on cells.

In light of the above, Applicants respectfully request reconsideration and withdrawal of the outstanding rejections under 35 U.S.C. § 103.

On the basis of the amendments and remarks presented herein, we believe that this application is now in condition for immediate allowance and respectfully request the Examiner to withdraw the outstanding rejections and pass this application to issue.

Respectfully submitted,

FLEHR HOHBACH TEST
ALBRITTON & HERBERT LLP

Jean P. Prunelle REG NO: 35,081
FOR: Walter H. Dreger
Reg. No. 24,190

Four Embarcadero Center
Suite 3400
San Francisco, CA 94111-4187
Telephone: (415) 781-1989